

What is the effect of aerobic exercise intensity on cardiorespiratory fitness in those undergoing cardiac rehabilitation? A systematic review with meta-analysis

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Abstract

Objective Assess the role of exercise intensity on changes in cardiorespiratory fitness (CRF) in patients with cardiac conditions attending exercise-based cardiac rehabilitation.

Design Systematic review with meta-analysis.

Data sources MEDLINE, Embase, CINAHL, SPORTDiscus, PsycINFO and Web of Science.

Eligibility criteria for selection Studies assessing change in CRF (reported as peak oxygen uptake; $\dot{V}O_{2peak}$) in patients post-myocardial infarction and revascularisation, following exercise-based cardiac rehabilitation. Studies establishing $\dot{V}O_{2peak}$ via symptom-limited exercise test with ventilatory gas analysis and reported intensity of exercise during rehabilitation were included. Studies with mean ejection fraction <40% were excluded.

Results 128 studies including 13,220 patients were included. Interventions were classified as moderate, moderate-to-vigorous or vigorous intensity based on published recommendations. Moderate and moderate-to-vigorous intensity interventions were associated with a moderate increase in *relative* $\dot{V}O_{2peak}$ (standardised mean difference \pm 95% CI = 0.94 ± 0.30 and 0.93 ± 0.17 , respectively), and vigorous-intensity exercise with a large increase (1.10 ± 0.25). Moderate and vigorous intensity interventions were associated with moderate improvements in *absolute* $\dot{V}O_{2peak}$ (0.63 ± 0.34 and 0.93 ± 0.20 , respectively), whereas moderate-to-vigorous intensity interventions elicited a large effect (1.27 ± 0.75). Large heterogeneity among studies was observed for all analyses. Subgroup analyses yielded statistically significant, but inconsistent, improvements in CRF.

Conclusion Engagement in exercise-based cardiac rehabilitation was associated with significant improvements in both absolute and relative $\dot{V}O_{2peak}$. Although exercise of vigorous intensity produced the greatest pooled effect for change in relative $\dot{V}O_{2peak}$, differences in pooled effects between intensities could not be considered clinically meaningful.

Registration Prospero CRD42016035638.

Introduction

Cardiovascular disease remains the largest cause of morbidity and mortality globally, with almost half of all cardiovascular deaths attributable to coronary artery disease¹. While mortality rates from coronary artery disease have steadily declined over the past decade, an ageing population coupled with improved treatment and management has led to a growing population who have survived a myocardial infarction (MI) or have undergone secondary preventative procedures, including percutaneous coronary intervention (PCI) or coronary artery bypass (CABG)¹. For these patients,

cardiac rehabilitation facilitates a systematic and multidisciplinary approach to improve functional capacity and health-related quality of life^{2 3}, reduce cardiovascular mortality and ease financial burden by lowering rehospitalisation rates⁴.

Exercise training has long been a cornerstone of cardiac rehabilitation programmes⁵. The most notable benefit is improved cardiorespiratory fitness (CRF), which remains the single strongest independent predictor of all-cause and cardiovascular-related mortality and morbidity⁶.

Cardiorespiratory fitness is typically defined as an individual's maximal oxygen uptake ($\dot{V}O_{2max}$), which represents the integrated functioning of the pulmonary, cardiovascular and muscular systems to uptake, transport and use oxygen for metabolic processes⁷. The assessment of $\dot{V}O_{2max}$ requires a plateau in oxygen consumption despite increases in exercise intensity. However, for a variety of reasons, a plateau in oxygen consumption is often not observed, such as the premature termination of testing due to ischemia. In such circumstances the term peak oxygen uptake ($\dot{V}O_{2peak}$) has been used to denote the highest rate of oxygen consumption achieved during cardiopulmonary exercise testing (CPET)⁷. The $\dot{V}O_{2peak}$ is shown to be strongly associated with future fatal and non-fatal cardiovascular events in both healthy and unhealthy men⁸, while improvements in CRF also underpin reductions in all-cause and cardiovascular-related mortality risk^{9 10}.

The dose response (i.e. intensity, duration and frequency) of aerobic exercise remains largely unclear. As duration and frequency are mainly functions of patient behaviour and service access, exercise intensity is one key physiological element related to individual patient function and risk, and thus forms an important focus for the rehabilitation practitioner.

A mean improvement in relative $\dot{V}O_{2peak}$ of $5.4 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (1.55 metabolic equivalents; METs) is possible during cardiac rehabilitation¹¹. However, the intensity required to achieve these improvements is unclear. In over 5,500 patients with heart failure, greater improvements in CRF were observed following high intensity exercise (≥ 9 METs) when compared with moderate (3-6 METs) or vigorous (6-9 METs) intensities¹². There is also a positive association between the number of exercise sessions completed and change in CRF¹³.

Further complexity is added given the plethora of methods to establish, prescribe and regulate exercise intensity, leading to varied individual adaptations^{14 15}. Despite a large evidence base for the efficacy of prescriptions based on indices of heart rate (HR) or $\dot{V}O_2$, these approaches often lead to large training ranges and ignore individual metabolic responses. Individualised methods, such as threshold-based prescriptions, are becoming increasingly popular, with preliminary evidence suggesting an attenuation of inter-individual responses^{14 16}. However, for many programmes, the use

of CPET to determine individual training threshold is not available¹⁷, thus large training ranges reflecting 50-75% $\dot{V}O_{2peak}$, prescribed using target HRs, are often the norm in clinical practice.

We aimed to investigate the effect of aerobic exercise intensity on changes in CRF in patients completing cardiac rehabilitation and to compare CRF responses to interventions of similar intensities across various methods of determining exercise intensity.

Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁸. The aims, eligibility criteria and analytical methods were designed *a priori* and registered with PROSPERO (CRD42016035638). Considering the number of studies included, this review employed quantitative methods to synthesise the literature and address the research questions, as opposed to a qualitative synthesis as indicated in the initial PROSPERO registration.

Criteria for study selection

Studies were included if they met the following criteria: (1) full length article in English published in a peer-reviewed journal, (2) experimental, quasi-experimental or cohort design, (3) participants were referred for cardiac rehabilitation following MI or revascularisation surgery (CABG or PCI), (4) intervention involved some form of aerobic exercise training, and (5) CRF at baseline and post-intervention was evaluated via analysis of expired air during a maximal (or symptom-limited) cardiopulmonary exercise test.

Studies were excluded if: (1) participants had documented heart failure or arrhythmia, (2) group mean ejection fraction (EF) <40%, (3) study targeted a specific comorbidity (e.g. diabetes, chronic obstructive pulmonary disease and stroke), (4) intervention involved swimming as the predominant mode of exercise or prescribed resistance exercises only. Studies with interventions lasting less than eight sessions or longer than 6 months were also excluded. These criteria were used to ensure the included studies reflected Phase II (outpatient) rehabilitation programmes; those less than eight sessions were considered Phase I (inpatient) rehabilitation and those longer than six months considered Phase III (maintenance) programmes.

Studies were required to detail the exercise prescription, including the frequency, intensity and duration of each session, mode of exercise and the overall length of the intervention.

Studies reporting sample size and the mean and SD for $\dot{V}O_{2peak}$ at both pre-intervention and post-intervention were included in quantitative synthesis.

Search strategy

A search of the MEDLINE, Embase, CINAHL, PsycINFO, SPORTDiscus and Web of Science electronic databases was conducted from their respective inception through April 2016. Database updates were then monitored for eligible publications until September 2017. Search terms were developed by the lead author and reviewed by experts on the research team. The search strategy (online supplementary material 1) combined keywords describing 'condition' (e.g. MI), 'intervention' (e.g. rehabilitation and exercise) and 'outcome' (e.g. fitness and $\dot{V}O_{2\max}$). Category-based search headings reflecting the keywords were also used where relevant. Database searches were not limited at any stage.

Study selection and data extraction

Database searches were conducted by the lead reviewer. Following removal of duplicates, two reviewers independently screened titles and abstracts, with full-text articles assessed against the inclusion/exclusion criteria. Disagreements during screening were resolved by consensus.

Where multiple articles reported on the same sample, or an update from the same study, we included the article with the larger sample size.

Data extraction was performed by the lead reviewer, with a random selection of 15 studies independently confirmed by a second reviewer. All data were extracted at the participant group level. Data extracted included: participant characteristics (age, sex, primary diagnosis, time since event and EF), description of the exercise testing protocol, and description of the intervention (session frequency and duration, intervention length, exercise modality, resistance training, type of training (interval/continuous), supervision (clinic/home) and intervention type (exercise only/comprehensive)). The intensity of aerobic exercise, the basis of exercise intensity (e.g. $\dot{V}O_{2\text{peak}}$ (% $\dot{V}O_{2\text{peak}}$), HR reserve (%HR_{reserve})) and how intensity was regulated within each session (e.g. HR, work rate, etc.) were also extracted. $\dot{V}O_{2\text{peak}}$ at baseline and post-intervention was extracted to assess change in CRF. Where possible, outcomes were extracted in relative ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and absolute ($\text{L}\cdot\text{min}^{-1}$) terms. Outcomes reported in METs were converted to relative terms ($\text{METs} \times 3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).

Where data were missing or required further clarification, attempts were made to contact corresponding authors.

Risk of bias

Risk of bias was assessed by the lead reviewer using a modified version of the McMaster Critical Review Form for Quantitative Studies¹⁹. The critical appraisal tool retained five domains of the

McMaster tool, adding three categories to explore the process of controlling/randomisation, quality of reporting the exercise intervention, and reporting attendance and compliance with the exercise intervention (Supplementary Material 2). No studies were excluded based on risk of bias assessment.

Data treatment and analysis

Each cardiac rehabilitation intervention was classified as having prescribed either light, moderate or vigorous intensity aerobic exercise, based on cut-offs proposed by the American College of Sports Medicine (ACSM)^{20 21} (Table 1). Where a study reported an intensity spanning the moderate and vigorous categories (e.g. 60-70% $\dot{V}O_{2peak}$), it was classified as 'moderate-to-vigorous'. Studies reporting exercise based on ventilatory threshold were classified as either moderate (below ventilatory threshold) or moderate-to-vigorous (at or above ventilatory threshold).

Table 1. Classification of exercise intensity based on physiological and perceived exertion responses

	% $\dot{V}O_{2max}$	%HR _{peak}	%HR _{reserve} or % $\dot{V}O_{2reserve}$	Perceived exertion*
Light	37–45	57–63	30–39	RPE 9–11
Moderate	46–63	64–76	40–59	RPE 12–13
Vigorous	64–90	77–95	60–89	RPE 14–17
Near-maximal to maximal	≥91	≥95	≥90	RPE ≥18

Table adapted from ACSM²⁰ and Garber et al.²¹.

*as per the Borg 6–20 RPE scale.

ACSM, American College of Sports Medicine; %HR_{peak}, percentage of peak heart rate; %HR_{reserve}, percentage of heart rate reserve; RPE, rating of perceived exertion; % $\dot{V}O_{2max}$, percentage of maximal oxygen uptake; % $\dot{V}O_{2reserve}$, percentage of oxygen uptake reserve.

Standardised mean difference (SMD) was calculated for each study for the change in $\dot{V}O_{2peak}$ over the intervention using the pooled between-subject SD at both time points^{22 23}. Effects were quantified as trivial (<0.20), small (0.21 – 0.60), moderate (0.61 – 1.20), large (1.21 – 2.00) and very large (>2.00)²⁴ with the precision of effect size estimates assessed using 95% CIs. Pooled SMD was back-transformed using the pooled between-subject SD at baseline within each intensity category.

Random-effects meta-analysis was performed at the participant group level using STATA (version 14; Stata Corp., TX), with estimates of homogeneity derived using the inverse variance method. A

random-effects model was used in light of the heterogeneity between studies regarding the characteristics of included participants and in the structure of the cardiac rehabilitation programmes^{22,23}. Significant results were assumed where $p < .05$.

Where studies did not report the SD for the mean change in $\dot{V}O_{2peak}$ across the intervention, the SE of the mean differences was imputed based on the correlation between pre-intervention and post-intervention outcomes, as per Elbourne et al.²⁵ The imputed SE was then used to calculate the 95% CI for the standardised effect of each study. For outcomes expressed as change in relative $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), a correlation of $r = 0.54$ from a similar meta-analysis¹¹ was used. As no studies were identified reporting a correlation for outcomes expressed as change in absolute $\dot{V}O_{2peak}$ ($\text{L}\cdot\text{min}^{-1}$), an estimated correlation of $r = 0.50$ was used. A sensitivity analysis was performed using estimated correlations of $r = 0.30$ and 0.70 , however these did not significantly alter the outcomes and are not presented here.

Separate meta-analyses were performed for each intensity category, with each category further split into subgroups based on the variable used to determine exercise intensity. To assess the effect of potential outlier studies, studies with an SMD of two or more SDs above/below the subgroup pooled effect were removed and pooled SMD recalculated.

Statistical heterogeneity was assessed using the I^2 and Cochran's Q statistics²⁶. To explore potential sources of heterogeneity, random-effects meta-regression using a maximum likelihood function was performed using pre-selected moderator variables. All moderators were determined *a priori* based on potential causal mechanisms and significance in previous literature. Moderators fell into two categories: participant characteristics (age, sex, principle diagnosis, and baseline CRF) or intervention/study characteristics (intervention length and frequency, number of sessions, exercise modality (aerobic only or combined resistance), study design (clinical trial or cohort) and risk of bias score).

Publication bias was assessed using the Stata packages *metabias*, to calculate Egger's test for asymmetry, and *metafunnel*, to produce funnel plots of SE against the SMD.

Results

Database searches identified 6 091 records with duplicates removed. The PRISMA flow diagram is presented in Figure 1. One hundred twenty-eight articles were included for review, with 113 included in quantitative synthesis. Summary table of study characteristics and references of included studies are provided as online supplementary materials 3 and 4, respectively. Agreement in data

extraction by the two authors for a random selection of 15 studies was excellent, with 99.0% agreement in >500 extracted data points.

Study characteristics

Risk of bias

Individual outcomes for risk of bias are provided in online supplementary material 5. Intraclass correlation coefficient for absolute agreement in appraisal scores for randomly selected 15 studies was $r = .91$, demonstrating excellent agreement between authors. The most common concern was a lack of reporting of the validity/reliability of outcome measures (equipment and/or procedures). In addition, the majority of studies did not report the proportion of CPETs that were terminated prematurely due to symptoms, and few adequately reported compliance with the exercise training protocol, specifically in quantifying compliance with prescribed exercise intensities.

Participants

There were 196 individual participant groups, comprising 13,220 participants undergoing exercise-based cardiac rehabilitation (Table 2).

Most groups (116/196) included a mix of men and women, where women typically accounted for 4–42% of the group and approximately 17% of all participants. Forty-one groups comprised only men and three groups recruited only female participants²⁷. Sex was not reported for 36 groups.

Majority of groups comprised solely of patients post-MI (81/196), with 32 groups post-CABG and 12 post-PCI. Eight groups underwent valvular repair/replacement. The remaining 58 groups, predominantly from studies of cohort design, included a mix of conditions/treatments.

Mean sample age (58.4 ± 4.9 y) was lower in groups solely of patients following MI (57.0 ± 4.1 y) and PCI (53.6 ± 5.0 y), compared with those following CABG (60.4 ± 4.0 y) or mixed pathologies (59.5 ± 5.6 y). Seven studies^{28–34} did not report age.

Baseline EF was reported for only 46% of patient groups (87/196 groups) and was lower in groups of MI ($51.5 \pm 5.4\%$) and mixed pathologies ($52.8 \pm 4.7\%$), compared with CABG ($58.1 \pm 4.9\%$).

227 Table 2. Characteristics of included studies

	n or mean \pm SD (range)
Study parameters (n = 121)^a	
Total patients	13,220
Patient group parameters (n = 196)^b	
Age, y	58.4 \pm 4.9 (45.3 – 75.0)
EF, %	53.7 \pm 5.6 (42.4 – 67.0)
Sex	
Male	41
Female	3
Mixed (%F)	116 (17.1 \pm 7.2)
Did not report	36
Primary diagnosis	
Post-MI	81
CABG only	32
PCI only	12
CABG/PCI	5
VR	8
Mix	55
Rehabilitation programme parameters (n = 150)^c	
Intensity	
Light	2
Moderate	18
Moderate-to-vigorous	52
Vigorous	68
Unable to categorise	10
Length, weeks	11.0 \pm 6.4
<6	24
6	21
6-11	26
12	58
>12	21
Frequency, sessions/week	3.3 \pm 1.8
1-2	22
3-4	106
5-7	15
>7	5
Supervision	
Clinic	133
Home	8
Mixed	8
Intervention type	
Comprehensive	33
Exercise only	117
Training type	
Continuous	133
Interval	14
Mixed	3
Exercise modality	
Aerobic only	124
Aerobic & resistance	26

228 EF, ejection fraction; %F, percent female; MI, myocardial infarction; CABG,
 229 coronary artery bypass graft; PCI, percutaneous coronary intervention; VR,
 230 valve repair/replacement.

231 n for section refers to number of ^aparticipants, ^bpatient groups,

232 ^crehabilitation programmes.

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Interventions

The included studies reported on 150 exercise-based cardiac rehabilitation interventions (Table 2). Interventions were between 2 and 26 weeks in length, with 1.5-14 exercise sessions per week. While most studies reported a precise intervention length, four studies reported large ranges (e.g. 1-4 weeks³⁵⁻³⁷ and 3-5 months³¹) and two studies reported unclear endpoints, including 'approx. 3 months'³⁸ or 'at least 75 sessions'³⁹. Frequency was not reported by two studies^{40 41}.

Interventions were typically conducted in a clinic/outpatient setting (133/150 interventions; 88%), supervised by a physician, nurse, physiotherapist or exercise physiologist/specialist, and eight interventions prescribed unsupervised/home exercise. Supervision was unclear for one intervention⁴².

Twenty-two per cent of interventions (33/150) were comprehensive, including counselling/risk factor management strategies in addition to structured exercise.

Exercise prescription and regulation

Exercise training was typically continuous (133/150; 89%) as opposed to interval (14/150) or a mixed training (3/150). Eleven interval training interventions followed a 4x4 min protocol, using either treadmill (n = 7), cycle ergometer (n = 6), home walking (n = 2) or group circuit (n = 1). One intervention⁴³ followed a 10x1 min protocol (1 min rest) prescribing 85 – 108% peak work-rate on a cycle ergometer. Two studies^{44 45} did not report the interval protocol used.

Sixty-five interventions established exercise intensity using HR_{peak} elicited during baseline CPET; as either percentage of HR_{peak} (% HR_{peak} ; n = 38) or percentage of $HR_{reserve}$ (% $HR_{reserve}$; n = 27).

Thirty-five interventions established intensity using $\dot{V}O_{2peak}$ from the baseline CPET (% $\dot{V}O_{2peak}$). Thirty interventions prescribed individualised intensities based on ventilatory threshold (%VT). Intensity was typically regulated using HR calculated to elicit target $\dot{V}O_2$. It was unclear how intensity was regulated in twelve interventions.

Perceived exertion was used to regulate exercise intensity in two interventions, using the Borg 6-20 rating of perceived exertion scale⁴⁶ and Borg CR10 scale⁴⁷.

Only 22 interventions included a process for revising exercise prescriptions during the intervention, and resistance exercises were included in 26 interventions.

Exercise intensity

Based on the ACSM cut-points^{20 21}, two interventions^{48 49} prescribed light-intensity exercise (1%), 18 interventions prescribed moderate-intensity exercise (12%) and 52 prescribed vigorous intensity exercise (35%). Sixty-eight interventions (45%) prescribed a range of intensities that placed them within both the moderate and vigorous categories.

Eight interventions, from seven studies^{36 50-55}, were not classified as they did not provide sufficient detail about the intensity of exercise. Two interventions were based on peak work-rate⁴³.

Meta-analysis

Ten groups (eight studies^{36 43 50 52-55}) where exercise intensity could not be classified, and two groups^{48 49} that prescribed light-intensity exercise were excluded from quantitative synthesis. A further ten groups (seven studies⁵⁶⁻⁶¹) were excluded due to missing data. Random-effects meta-analysis was performed on 174 participant groups, representing 130 cardiac rehabilitation interventions. Pooled intervention effects are presented in Figures 2-5, with outcomes following back-transformation presented in Table 3.

Change in relative $\dot{V}O_{2peak}$

Relative $\dot{V}O_{2peak}$ significantly increased in all intensity categories. Moderate (Figure 2) and moderate-to-vigorous (Figure 3) interventions were associated with a moderate increase in relative $\dot{V}O_{2peak}$ (SMD \pm 95%CI = 0.94 ± 0.30 , $p < 0.001$ and 0.93 ± 0.17 , $p < 0.001$, respectively), equating to a mean (\pm 95% CI) increase of 4.1 ± 2.3 and 4.9 ± 0.9 mL \cdot kg⁻¹ \cdot min⁻¹, respectively. Vigorous interventions (Figure 4) were associated with a large increase in relative $\dot{V}O_{2peak}$ (1.10 ± 0.25 , $p < 0.001$), equating to an increase of 5.5 ± 1.3 mL \cdot kg⁻¹ \cdot min⁻¹. While effects were all statistically significant, they were also highly heterogeneous, with I^2 values of 93.9%, 98.1% and 95.3% ($p < 0.001$) for the three intensities, respectively.

294 Table 3. Summary of pooled effects for change in $\dot{V}O_{2peak}$ following back-transformation

	Relative $\dot{V}O_{2peak}$ (mL·kg ⁻¹ ·min ⁻¹)	Absolute $\dot{V}O_{2peak}$ (L·min ⁻¹)
Moderate	4.1 (2.7, 5.4)	0.22 (0.10, 0.33)
%HR _{peak}	1.8 (-0.4, 4.1)	
%HR _{reserve}	3.9 (2.0, 5.8)	0.20 (0.01, 0.39)
% $\dot{V}O_{2peak}$	6.1 (2.9, 9.3)	0.27 (0.19, 0.35)
%VT	3.5 (2.6, 4.5)	
Moderate-to-vigorous	4.9 (4.0, 5.8)	0.53 (0.22, 0.84)
%HR _{peak}	3.1 (2.7, 3.6)	0.13 (0.03, 0.23)
%HR _{reserve}	14.6 (5.3, 23.8)	1.39 (0.79, 1.99)
% $\dot{V}O_{2peak}$	7.3 (4.7, 9.9)	0.55 (0.02, 1.08)
%VT	4.3 (3.8, 4.8)	0.28 (0.16, 0.39)
RPE	2.9 (1.5, 4.4)	
Vigorous	5.5 (4.3, 6.7)	0.44 (0.35, 0.54)
%HR _{peak}	4.3 (2.1, 6.6)	0.23 (0.16, 0.31)
%HR _{reserve}	3.7 (2.9, 4.5)	0.37 (0.28, 0.45)
% $\dot{V}O_{2peak}$	8.3 (5.1, 11.5)	0.66 (0.23, 1.09)

295 Back-transformation used the pooled between-subject SD at baseline for studies included within
 296 each intensity category.

297 Subgroup analyses

298 *Moderate intensity.* Interventions based on % $\dot{V}O_{2peak}$ produced the largest increase, and %HR_{reserve}
 299 and %VT moderate increase, in pooled $\dot{V}O_{2peak}$. % $\dot{V}O_{2peak}$ and %HR_{reserve} demonstrated significant
 300 heterogeneity ($I^2 = 93-95\%$). Interventions based on %HR_{peak} produced a small, but non-significant,
 301 increase.

302 *Moderate-to-vigorous intensity.* Interventions based on % $\dot{V}O_{2peak}$ produced a large increase in pooled
 303 $\dot{V}O_{2peak}$. Visual inspection of Figure 3C suggests that this subgroup also produced highly varied
 304 responses ($I^2 = 97.8\%$). Interventions based on ventilatory threshold produced a moderate increase
 305 and, while still significant, demonstrated lower heterogeneity ($I^2 = 84.5\%$). Interventions based on
 306 %HR_{peak} and perceived exertion produced a small increase.

307 *Vigorous intensity.* Interventions based on % $\dot{V}O_{2peak}$ produced the largest increase in pooled $\dot{V}O_{2peak}$
 308 but demonstrated high heterogeneity ($I^2 = 97.1\%$). Interventions based on %HR_{peak} or %HR_{reserve}
 309 produced a moderate increase and exhibited less heterogeneity ($I^2 = 74-95\%$).

310 Change in absolute $\dot{V}O_{2peak}$

311 Absolute $\dot{V}O_{2peak}$ significantly increased in all intensity categories (Figure 5). Moderate and vigorous
 312 interventions produced a moderate increase in absolute $\dot{V}O_{2peak}$ (0.63 ± 0.34 , $p < 0.001$ and $0.93 \pm$

0.20, $p < 0.001$, respectively), equating to an increase of 0.22 ± 0.12 and 0.44 ± 0.10 L·min⁻¹, respectively. Moderate-to-vigorous interventions produced a large increase in absolute $\dot{V}O_{2peak}$ (1.27 ± 0.75 , $p = 0.001$), equating to an increase of 0.53 ± 0.31 L·min⁻¹. There was significant heterogeneity present in all three categories, with I^2 values of 79.5%, 99.2% and 93.6%, respectively.

Subgroup analyses

Moderate intensity. Interventions based on %HR_{reserve} and % $\dot{V}O_{2peak}$ produced a small-to-moderate increase in absolute $\dot{V}O_{2peak}$.

Moderate-to-vigorous intensity. Large differences were observed across subgroups for moderate-to-vigorous interventions. Interventions based on %HR_{reserve} produced a very large increase but demonstrated high heterogeneity ($I^2 = 98.7\%$) and contained three groups from the same study who completed the same intervention. Interventions based on % $\dot{V}O_{2peak}$ produced a large increase; however, this appeared to be driven primarily by a single outlier group that, when removed, lowered the pooled effect from an SMD of 1.32 ± 1.26 to 0.51 ± 0.25 . Interventions based on %VT produced a moderate increase, with significant heterogeneity. Only one study used perceived exertion as the basis of exercise prescription and did not report a significant change in absolute $\dot{V}O_{2peak}$.

Vigorous intensity. Interventions based on % $\dot{V}O_{2peak}$ and %HR_{reserve} produced a large and moderate increase in absolute $\dot{V}O_{2peak}$ respectively, with significant heterogeneity ($I^2 = 91-96\%$). This appeared to be primarily driven by few outlier groups. While the removal of one group for the %HR_{reserve} and two groups from the % $\dot{V}O_{2peak}$ subgroups did not significantly lower the level of heterogeneity within each subgroup, the pooled effect of the % $\dot{V}O_{2peak}$ was reduced from an SMD of 1.38 ± 0.90 to 0.77 ± 0.40 . Interventions based on %HR_{peak} produce a small increase in $\dot{V}O_{2peak}$.

Meta-regression

Overall, there was a lack of consistency in the ability of moderator variables to explain additional heterogeneity (Table 4). Baseline CRF significantly predicted the change in relative $\dot{V}O_{2peak}$ for the moderate and vigorous interventions ($R^2_{adj} = 43.8\%$ and 18.1% , respectively) and was the only significant predictor of absolute $\dot{V}O_{2peak}$ ($R^2_{adj} = 21.7\%$ for vigorous interventions). Vigorous interventions comprising only men or women reported greater outcomes compared with mixed sex ($R^2_{adj} = 26.4\%$). Mixed supervision interventions were associated with greater increase in relative $\dot{V}O_{2peak}$ for moderate-to-vigorous and vigorous interventions. Risk of bias score was associated with outcomes for moderate-to-vigorous interventions.

Table 4. Outcomes of meta-regression analyses for heterogeneity

		Moderate	Moderate-to-vigorous	Vigorous
Participant characteristics				
Age		0.053 (-0.025, 0.131)	-0.021 (-0.055, 0.013) -0.198 (-0.410, 0.014) [†]	-0.027 (-0.102, 0.048) -0.090 (-0.227, 0.046)
Sex	Mixed	REF	REF	REF
	Male	-0.410 (-1.312, 0.493)	-0.110 (-0.558, 0.339) -0.648 (-2.723, 1.428)	0.759 (0.224, 1.294) [‡] 0.338 (-0.491, 1.167)
	Female	NA	-0.347 (-1.984, 1.289) NA*	0.837 (-0.354, 2.029) NA*
Baseline $\dot{V}O_{2peak}$		-0.076 (-0.134, -0.019) [†]	-0.027 (-0.043, 0.029) -0.041 (-0.175, 0.093)	-0.065 (-0.120, -0.009) [‡] -0.091 (-0.170, -0.011) [‡]
Primary diagnosis	Post-MI	REF	REF	REF
	Revascularisation	-0.352 (-1.338, 0.634)	-0.228 (-0.621, 0.164) -0.649 (-2.414, 1.115)	-0.095 (-0.836, 0.646) 0.306 (-0.789, 1.401)
	Valve surgery	NA	-0.341 (-0.961, 0.278) NA*	NA* 0.005 (-2.110, 2.120)
	Mixed pathology	-0.444 (-1.315, 0.427)	-0.497 (-0.889, -0.106) [†] -1.298 (-3.720, 1.125)	0.560 (-0.096, 1.216) [†] 0.449 (-0.498, 1.395)
Intervention/study characteristics				
Intervention length		-0.009 (-0.056, 0.038)	-0.001 (-0.026, 0.024) 0.017 (-0.172, 0.207)	-0.022 (-0.070, 0.027) -0.032 (-0.097, 0.032)
Session frequency		-0.050 (-0.305, 0.205)	0.038 (-0.152, 0.227) 0.582 (-0.026, 1.190) [†]	-0.011 (-0.218, 0.195) 0.272 (-0.331, 0.875)
No. of sessions		-0.001 (-0.017, 0.014)	-0.001 (-0.008, 0.008) 0.010 (-0.018, 0.038)	-0.001 (-0.012, 0.010) -0.001 (-0.015, 0.012)
Exercise modality		NA	-0.285 (-0.618, 0.049) [†] -1.277 (-2.818, 0.263) [†]	-0.465 (-1.738, 0.807) -0.637 (-2.639, 1.365)
Exercise type		NA	0.443 (-0.634, 1.519) NA*	0.632 (-0.134, 1.397) 0.644 (-0.152, 1.441)
Supervision	Clinic	REF	REF	REF
	Home	0.176 (-1.200, 1.552)	-0.033 (-0.644, 0.577) -0.817 (-3.965, 2.331)	-0.490 (-2.048, 1.069) -0.455 (-1.900, 0.990)
	Mixed	NA	2.264 (1.227, 3.300) [‡] 1.759 (-1.406, 4.923)	0.489 (-1.070, 2.049) NA*
Intervention type		-0.496 (-1.146, 0.154)	-0.214 (-0.594, 0.166) -1.200 (-2.886, 0.486)	-0.178 (-0.907, 0.550) -0.637 (-2.084, 0.809)
Study design		-0.160 (-0.910, 0.589)	-0.205 (-0.530, 0.120) 1.234 (-0.247, 2.715) [†]	0.247 (-0.395, 0.889) 0.404 (-0.356, 1.164)
Risk of bias score		0.154 (-0.038, 0.346)	0.115 (0.015, 0.216) [‡] -0.383 (-0.961, 0.196)	0.114 (-0.079, 0.307) -0.027 (-0.203, 0.257)

[†]p < 0.10, [‡]p < 0.05. Values presented are β (95% CI for β). First row presents outcomes for difference in relative $\dot{V}O_{2peak}$ (mL·kg⁻¹·min⁻¹), second row presents difference in absolute $\dot{V}O_{2peak}$ (L·min⁻¹).

REF, reference category; NA, not available; NA*, subgroup omitted due to significant collinearity; MI, myocardial infarction.

Publication bias

There was no significant publication bias for outcomes expressed in either relative (Egger's test: $\beta = 1.70$, $p = .07$) or absolute $\dot{V}O_{2peak}$ ($\beta = 2.25$, $p = .21$) with all studies taken together (online supplementary material 6). However, there was significant publication bias for studies with vigorous interventions reporting absolute $\dot{V}O_{2peak}$ ($\beta = 4.82$, $p = .01$). No other subgroup analyses suggested publication bias (all $p > .05$).

Discussion

This review stratified pooled analyses by exercise intensity to provide a broad review of the effect of exercise intensity during exercise-based cardiac rehabilitation on changes in CRF. Foremost, our results support the role of exercise in patients following a cardiac event or surgery to improve CRF. Comparisons of pooled effects between intensity classifications suggested that vigorous intensity and moderate-to-vigorous intensity exercise may provide the greatest improvements in relative and absolute $\dot{V}O_{2peak}$, respectively. However, considering the significant and pervasive between study heterogeneity and overlap in 95% CIs, differences between intensities were not statistically significant. Further, differences were not considered clinically meaningful as back transformation of the SMD suggested that differences between intensities were, at most, only $1.4 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and $0.31 \text{ L}\cdot\text{min}^{-1}$ (for relative and absolute $\dot{V}O_{2peak}$, respectively).

Discrepancies between studies

It is interesting to note the conflicting findings between interventions reporting to prescribe moderate-to-vigorous intensity exercise, conferring the smallest improvement in relative $\dot{V}O_{2peak}$. A likely explanation for this is the inconsistency in intensity, duration and frequency that underpin the exercise prescriptions¹¹. Given the moderate-to-vigorous category comprised studies prescribing exercise intensities over a sizeable range, spanning both moderate and vigorous categories, it may be that the studies contained within the category are not directly comparable.

Previous reviews assessing the efficacy of cardiac rehabilitation have typically centred on outcomes associated with mortality, recurrent events/rehospitalisation or changes in primary risk factors such as cholesterol, blood pressure and smoking cessation^{3 62 63}. The first meta-analysis that investigated improvements in CRF following exercise-based cardiac rehabilitation reported a small improvement in CRF ($\text{SMD} \pm 95\% \text{CI} = 0.46 \pm 0.02$)⁶⁴. However, this review was limited to randomised controlled and quasi-experimental trials and thus may not reflect outcomes of interventions typically performed in a clinical setting where such control may not be feasible. The subsequent review by Sandercock et al.¹¹ included cohort studies and reported a larger increase in CRF (0.97 ± 0.17) following cardiac rehabilitation. However, this review excluded studies that used non-weight bearing

exercise (e.g. cycle ergometry) to assess CRF despite these modalities providing similar outcomes that are considered no less valid or reliable. Further, non-weight bearing exercise may be more desirable in a clinical setting where additional considerations, such as patient safety and function, equipment availability or simply to parallel training modality, may be of greater importance. Thus, excluding studies of non-weight bearing exercise may introduce a systematic source of bias. Our review included studies of both clinical trial and cohort designs, and placed no restrictions on exercise testing modality, allowing a broader review of the literature. Despite these differences, our findings were consistent with those reported by Sandercock et al.¹¹.

When interpreting these results, it is important to consider how exercise intensity was classified. We used a categorical based approach, where interventions were categorised according to the prescribed exercise intensity reported in each study based on the recommendations of the ACSM^{20 21}. There are two limitations with this approach. First, while some studies reported precise exercise intensities (e.g. 60% $\dot{V}O_{2peak}$), the majority reported wide ranges of intensity (e.g. 50-85% $\dot{V}O_{2peak}$). As these studies often spanned several categories, making them difficult to categorise, we coded an additional moderate-to-vigorous intensity category. In this category, participants were assumed to have undertaken similar training interventions, when in fact may have experienced quite different exercise prescriptions.

The second limitation was the inability to calculate a 'dose' for each intervention. A composite variable that considers intensity, frequency and time of sessions and duration of the intervention on a continuous scale may provide stronger associations with changes in CRF. Overall, compliance with prescribed exercise intensities was poorly reported, limiting the ability to accurately calculate exercise dose. This is especially important in studies prescribing large intensity ranges. Where studies did report compliance with the exercise prescription, there was no consistency, limiting the ability to compare between studies. For example, Moholdt et al.⁶⁵ prescribed exercise for two groups at 90% and 70% of HR_{peak} , and confirmed participants adhered to this prescription by reporting mean training HR of $92 \pm 5\%$ and $74 \pm 4\%$ HR_{max} , respectively. In contrast, Kraal et al.⁶⁶ reported the average time spent per session within the prescribed intensity range.

The different variables used to establish exercise intensity added complexity to analyses. While the variables were based on interrelated physiological constructs (e.g. HR and $\dot{V}O_2$), they are not directly comparable. Even in what appears to be the narrow domain of high-intensity interval training, there is much heterogeneity in clearly defining what high-intensity is. To elucidate potential differences between these prescription approaches, we performed subgroup analyses within each intensity. Although these analyses did not yield any consistent findings, they highlighted considerable

variability in outcomes for interventions based on $\% \dot{V}O_{2\text{peak}}$ that appeared to be consistent across intensities. Although unexpected, this finding is not surprising. Given $\dot{V}O_2$ is not an appropriate variable to regulate intensity during training, in practice prescriptions are converted to HR estimated to elicit the target $\dot{V}O_2$. This approach is confounded in a cardiac rehabilitation setting by medications⁶⁷ (e.g. β -blockers) that alter HR responses. This may cause a dissociation of the HR and $\dot{V}O_2$ relationship, where a small change in HR may result in varied and disproportionate changes to work rate or $\dot{V}O_2$.

Sources of heterogeneity

Significant heterogeneity in study outcomes was observed in this review. Meta-regression analyses performed to explore potential sources of heterogeneity yielded inconsistent findings. Baseline CRF was the only variable to consistently explain significant heterogeneity in outcomes for studies of moderate and vigorous intensity, but not moderate-to-vigorous interventions. In contrast to previous reviews^{11 64 68}, age, sex and exercise type (aerobic versus combined aerobic/resistance) were unable to explain differences between studies.

Furthermore, the frequency of exercise sessions was not a significant source of heterogeneity. This contrasts with a similar review of patients with heart failure⁶⁹ that concluded improvements in CRF were primarily determined by total energy expenditure across the intervention and higher session frequency associated with larger immediate improvements. Given the poor reporting of compliance with exercise prescription among studies, we were unable to perform similar analyses in estimating energy expenditure.

Limitations

We acknowledge several limitations. Only one author was responsible for data extraction and risk of bias assessment. This introduces a potential source of error and bias but agreement with a second author on data extraction and risk of bias assessment for a random test of 15 studies was high.

Further, this review included only studies with full-text published in English and may therefore have introduced a source of language bias. Of the full-text articles assessed for eligibility, 165 (24%) were excluded as they were not available in English.

The studies included in this review were predominantly of quasi-experimental design. While such study designs provide less rigour than the randomised controlled trial design, it provides clinical generalisability that must be lacking in tightly controlled 'efficacy' randomised controlled trials.

This review did not compare study outcomes to control participants who did not receive any form of exercise-based cardiac rehabilitation. As such conclusions drawn from the results presented here

reflect only the association between exercise intensity during cardiac rehabilitation and changes in CRF. Caution should therefore be taken when inferring the overall effectiveness of exercise-based cardiac rehabilitation interventions as a means of improving CRF over and above potential improvements simply from recovery. Similarly, differences in the change in CRF were assessed between studies of differing intensities, as opposed to between groups who received interventions of differing intensities within the same study. As such, the effect estimates presented here may be confounded by differences between the studies and may not have been identified through meta-regression.

We acknowledge the lack of data available for some analyses. For example, subgroup analyses for the pooled effect of moderate intensity programmes based on %HR_{peak} were based on two patient groups only, both of which were from the same study and completed the same intervention. Further, meta-regression analyses demonstrated larger effects in groups comprised solely of women compared with those of mixed sex, however interpretation of this outcome is limited given the few groups that only included women (n = 3). As such, we recommend caution when interpreting outcomes where a lack of available data may have limited analyses.

Implications and recommendations

In our systematic review, exposure to cardiac rehabilitation interventions with aerobic exercise training was associated with improvements in CRF. Although there were some differences between intensities, these were not statistically significant, nor were they considered clinically meaningful. However, we note that these findings are based on longitudinal outcomes between studies, not comparisons with non-active controls and thus may be confounded by differences in study characteristics.

There is a need for research concerning the most effective exercise prescription for improving CRF during cardiac rehabilitation. Of the 150 interventions, 138 established exercise prescriptions using HR or $\dot{V}O_2$ responses (incl. ventilatory threshold) that were regulated using HR. Although only two studies regulating exercise with perceived exertion were included^{46 47}, they produced improvements in CRF comparable with other regulatory methods. Given the potential limitations of HR-based prescriptions in this population, additional research is needed to further explore the efficacy of this prescription method.

There is a need for improved reporting among studies. Future research should include methods to appropriately describe the compliance of participants with the prescribed exercise intensity and attendance to exercise sessions. Further, studies should accurately report exercise protocols to allow for replication. As a minimum, studies should report the duration and protocols associated with

warm-up and cool-down procedures, as well as the duration and protocols associated with each modality used for aerobic exercise training. Where possible, studies should avoid providing a range, instead providing a specific and calculable duration.

Future reviews investigating the role of exercise-based cardiac rehabilitation should exclude studies that report poor compliance, or fail to report compliance, with attendance to exercise sessions and adherence to prescribed exercise.

Conclusion

Exercise-based cardiac rehabilitation is associated with significant improvements in CRF in patients following a cardiac event or surgery. Our review suggests that greater improvements in CRF may be conferred through prescription of more vigorous intensities. However, the additional improvements to CRF ($\approx 1.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) over the course of a cardiac rehabilitation intervention were not statistically significant and could not be considered clinically meaningful. While the findings of this review may provide a case for higher intensity training methods, such as high-intensity interval training, as part of a supervised cardiac rehabilitation intervention, these potential benefits should be considered in tandem with the potentially elevated risk of adverse events associated with higher intensities in this vulnerable population.

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Figure 1. Search results and selection of studies. CRF, cardiorespiratory fitness.

Figure 2. Effect of moderate intensity exercise during cardiac rehabilitation on change in relative $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Freq., frequency; SMD, standardised mean difference; IV, inverse variance; CI, confidence interval; SE, standard error; NS, not stated. Subgroups denote the variables from which exercise intensities were derived [e.g. an intensity of 70% in category a) Peak heart rate, is interpreted as 70% peak heart rate].

Figure 3. Effect of moderate-to-vigorous intensity exercise during cardiac rehabilitation on change in relative $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). For definitions and subgroups see Figure 2.

Figure 4. Effect of vigorous intensity exercise during cardiac rehabilitation on change in relative $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). For definitions and subgroups see Figure 2.

Figure 5. Effect of exercise intensity during cardiac rehabilitation on change in absolute $\dot{V}O_{2peak}$ ($\text{L}\cdot\text{min}^{-1}$). For definitions and subgroups see Figure 2.

Key Messages

What is already known

- Cardiorespiratory fitness (CRF) remains the single strongest predictor of all-cause and cardiovascular-related mortality, as well as future fatal and non-fatal coronary events. Improvements in CRF appear to underscore reductions in mortality risk.
- Exercise therapy during cardiac rehabilitation provides an opportunity to mitigate risk of rehospitalisation, reoccurrence and mortality.
- Recent reviews have highlighted the effectiveness of exercise-based cardiac rehabilitation to improve CRF, however little is known regarding the differential effects of prescribed exercise intensity.

What are the new findings

- Majority of cardiac rehabilitation studies report prescribing large ranges of exercise intensities based on heart rate responses to exercise.
- There was little consistency across studies in the change in CRF following cardiac rehabilitation.
- Vigorous intensity exercise during cardiac rehabilitation may provide greater benefits over moderate- or moderate-to-vigorous intensities, but additional benefits are unlikely to be clinically significant.

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Contributors

BLM contributed to the design of the study, literature search, data screening and extraction, risk of bias assessment, conducted all statistical analyses and managed all aspects of the manuscript preparation and submission. MJL contributed to the literature search, data screening and extraction, and risk of bias assessment, and contributed to writing and editing of the manuscript. KD, GP and RGE contributed to the study design, search strategy, statistical plan, and contributed to writing and

727 editing of the manuscript. JPB contributed to the search strategy, provided theoretical and practical
728 expertise, and contributed to the interpretation of findings and editing of the manuscript.

729 **Funding**

730 None declared.

731 **Competing interests**

732 None declared.

733 **Data sharing statement**

734 All data in this review are available in the journal in which they were published.

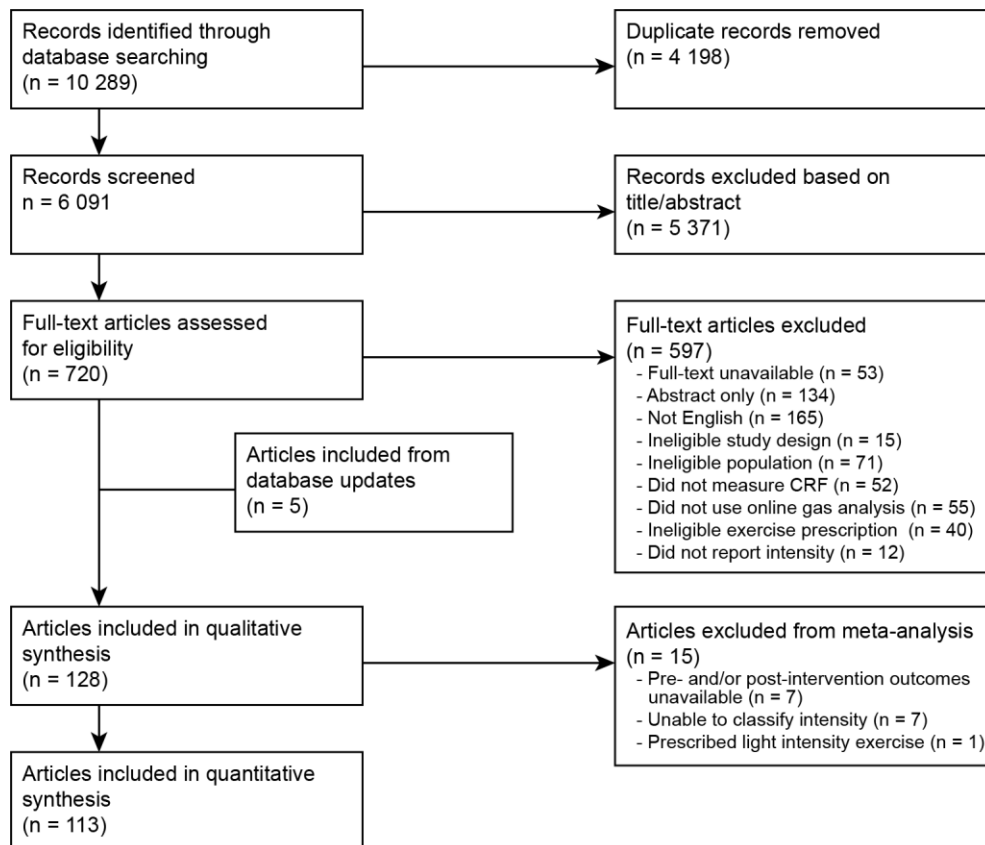


Figure 1. Search results and selection of studies. CRF, cardiorespiratory fitness.

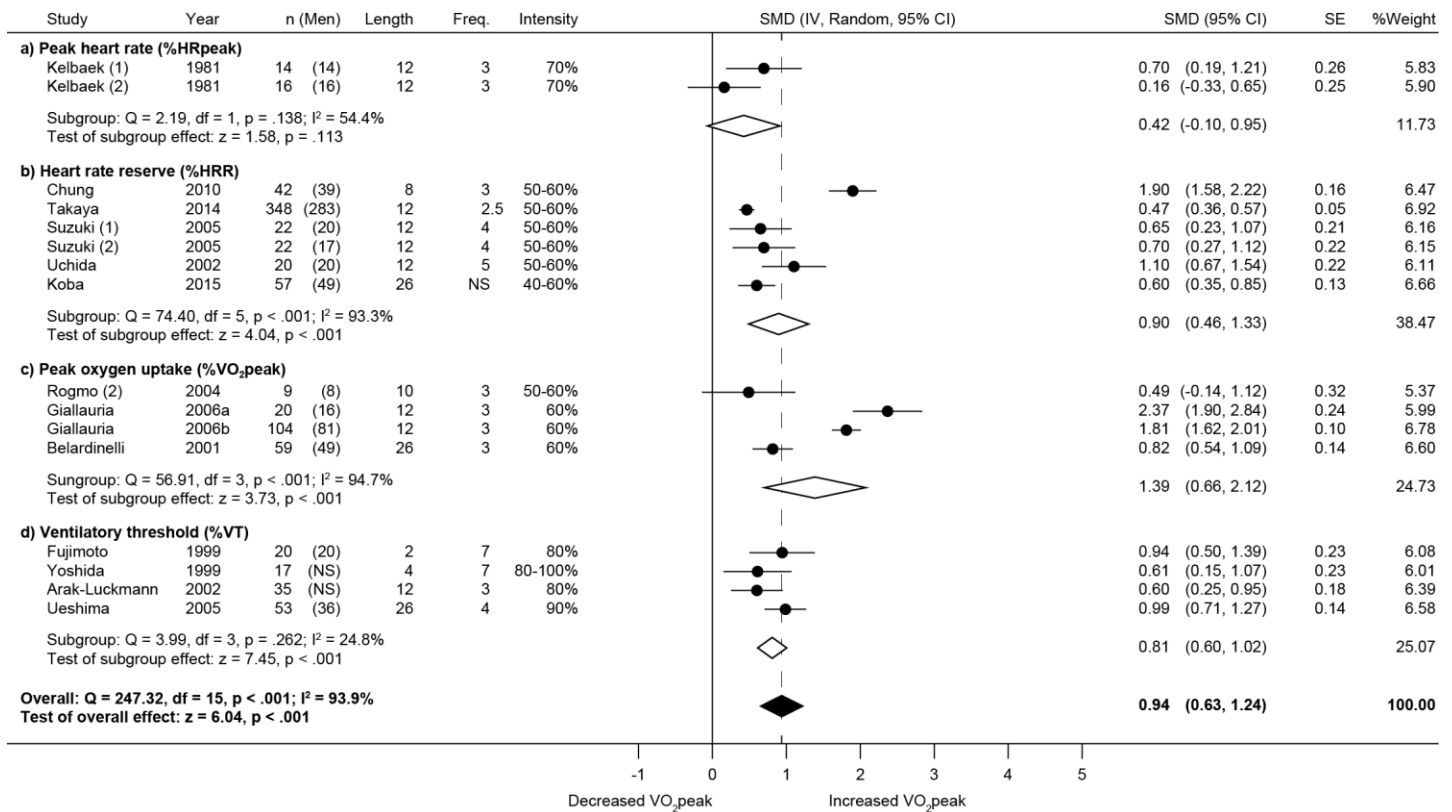


Figure 2. Effect of moderate intensity exercise during cardiac rehabilitation on change in relative $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Freq., frequency; SMD, standardised mean difference; IV, inverse variance; CI, confidence interval; SE, standard error; NS, not stated. Subgroups denote the variables from which exercise intensities were derived [e.g. an intensity of 70% in category a) Peak heart rate, is interpreted as 70% peak heart rate].

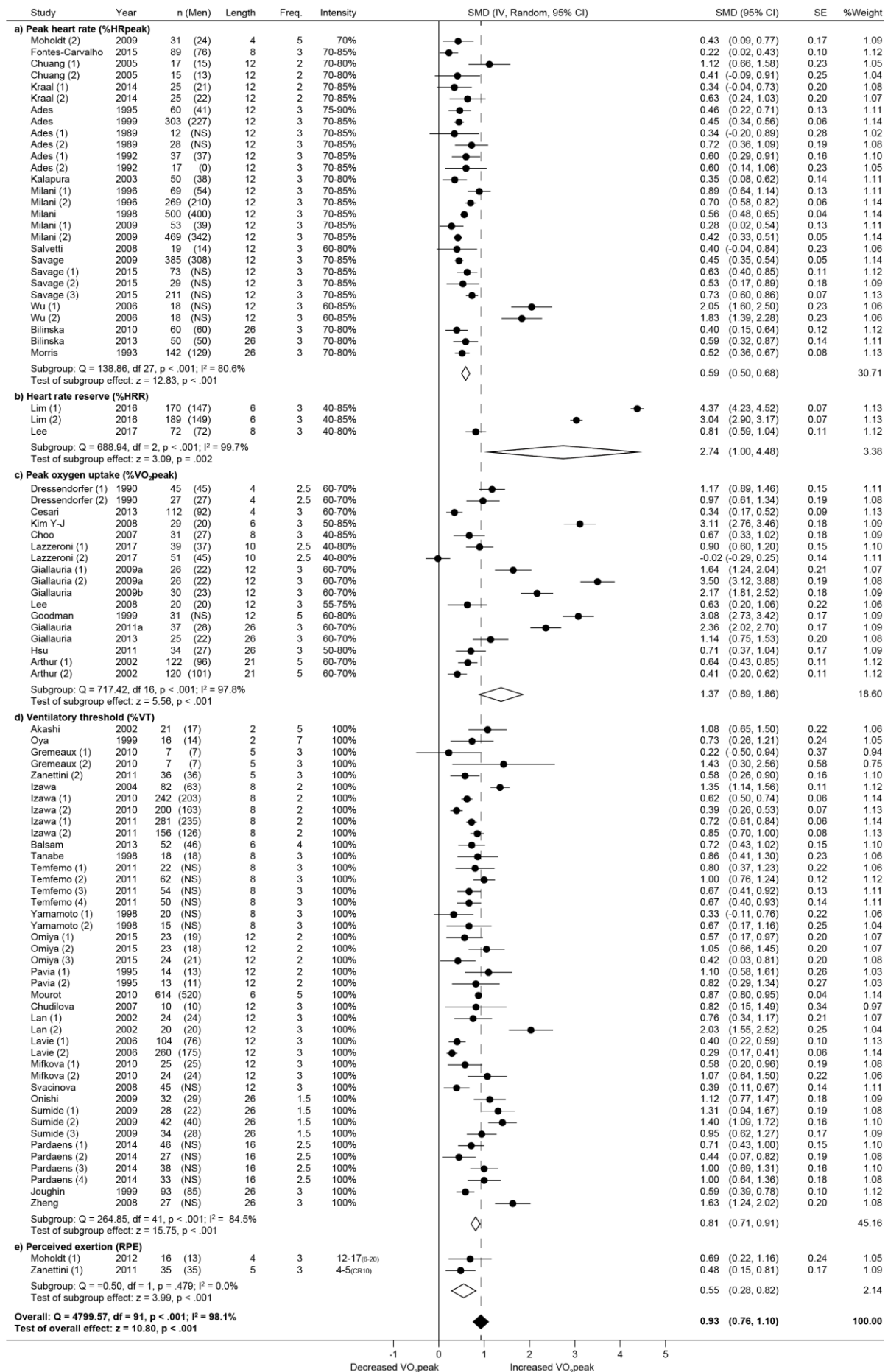


Figure 3. Effect of moderate-to-vigorous intensity exercise during cardiac rehabilitation on change in relative $\dot{V}O_{2peak}$ ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). For definitions and subgroups see Figure 2.

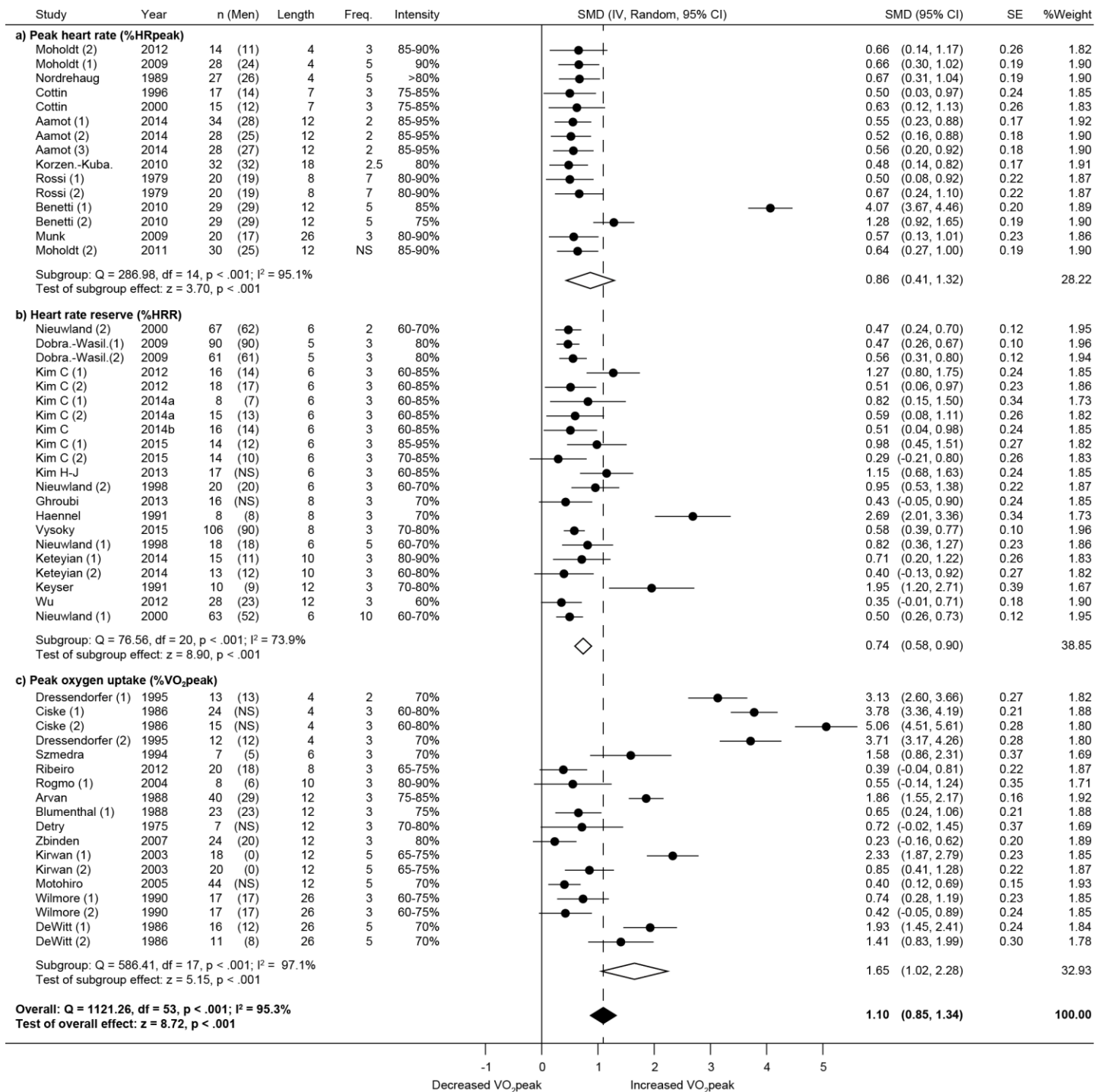


Figure 4. Effect of vigorous intensity exercise during cardiac rehabilitation on change in relative $\dot{V}O_{2peak}$ (mL·kg⁻¹·min⁻¹). For definitions and subgroups see Figure 2.

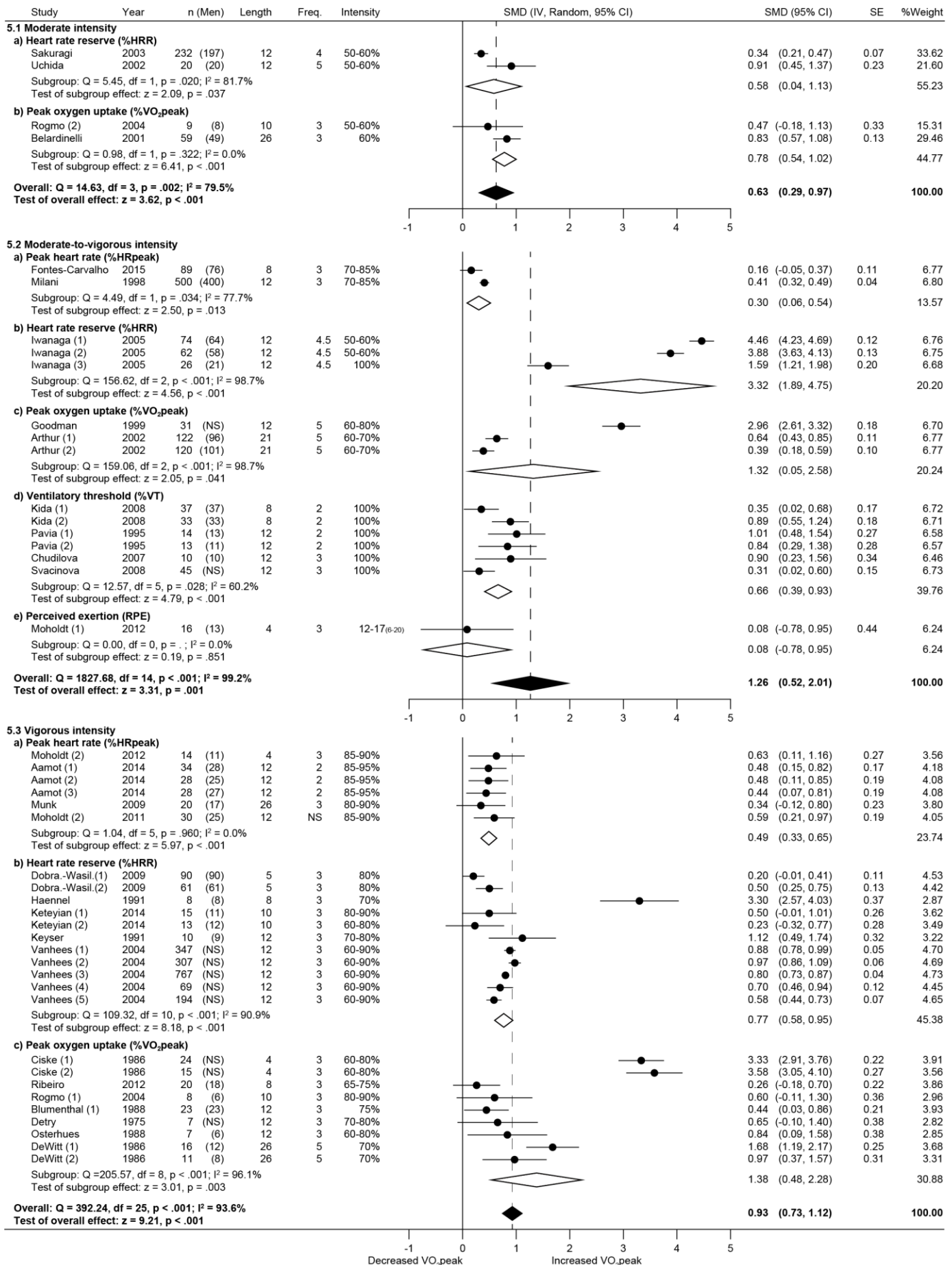


Figure 5. Effect of exercise intensity during cardiac rehabilitation on change in absolute $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$). For definitions and subgroups see Figure 2.